

Appl. No.: TBA  
Amdt. Dated: August 27, 2003

AMENDMENTS TO THE SPECIFICATION:

Please amend the title at page 1 as follows:

~~Skin Basement Membrane Formation Promoting Agent, Artificial  
Skin Formation Promoting Agent and Production Method for  
Artificial Skin~~

Agent Promoting the Formation of Skin Basement Membrane,  
Agents Promoting the Formation of Artificial Skin and Process for  
Producing Artificial Skin

Please add the following paragraph beginning at line 6 of  
page 1:

This application claims the priority of Japanese Patent  
Application No. 2000-87574, filed on March 27, 2000, which is  
incorporated herein by reference.

Please amend the paragraph beginning at line 4 of page 2 as  
follows:

The most powerful effect of the above external environment  
on skin aging is produced by ultraviolet rays present in  
sunlight, and these ultraviolet rays have clearly been  
established to be a factor that promotes aging. Ultraviolet rays  
are known to induce skin changes referred to as photoaging that

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[[58]] 38, 639-655). Ultraviolet rays have a diverse range of effects on the skin, including damage to genetic DNA, induced production of active oxygen, and more recently, induced production of matrix-metalloproteinases (Fisher, et al., Nature, 1966, 379, 335-339).

Please amend the paragraph beginning at line 9 of page 6 as follows:

Specific examples of matrix metalloproteinase inhibitors include substance CGS27023A ~~(N-hydroxy-2-[[[(4-methoxyphenyl)sulfonyl]3-picolyl]amino]-3-methylbutane amide hydrochloride)~~ N-hydroxy-2(R)-[[[(4-methoxyphenyl)sulfonyl](3-picolyl)amino]-3-methylbutanamide hydrochloride (J. Med. Chem. 1997, Vol. 40, p. 2525-2532), and MMP-inhibitor (p-NH<sub>2</sub>-Bz-Gly-Pro-D-Leu-Ala-NHOH) (FN-437) (BBRC, 1994, Vol. 199, p. 1442-1446).

Please amend the paragraph beginning at line 26 of page 11 as follows:

More specifically, examples of liquid oils include avocado oil, tsubaki oil, primrose oil, turtle oil, macadamia nut oil, corn oil, mink oil, olive oil, rape seed oil, egg yolk oil, sesame oil, persic oil, wheat germ oil, sasanqua oil, castor oil, linseed oil, safflower oil, cottonseed oil, perilla oil, soy bean oil, peanut oil, theine oil, kaya oil, rice bran oil, Chinese wood oil,

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Japanese wood oil, hohoba oil, germ oil, triglycerin, trioctanoic glycerin and triisopalmitic glycerin; examples of solid oils include cacao butter, coconut oil, horse tallow, hardened coconut oil, palm oil, beef tallow, goat tallow, hardened beef tallow, palm heart oil, pork tallow, beef bone tallow, haze heart oil, hardened oil, beef leg tallow, haze wax and hardened castor oil; examples of waxes include beeswax, candelilla wax, cotton wax, carnauba wax, bayberry wax, tree wax, spermaceti, montan wax, bran wax, lanolin, kapok wax, lanolin acetate, liquid lanolin, sugar cane wax, isopropyl lanolin fatty acid, hexyl laurate, reduced lanolin, jojoba wax, hard lanolin, shellac wax, POE lanolin alcohol ether, POE lanolin alcohol acetate, POE cholesterol ether, lanolin fatty acid polyethylene glycol and POE hydrogenated lanolin alcohol ether; and examples of hydrocarbon oils include liquid paraffin, ozokerite, squalene, pristan, paraffin, ceresin, squalene, Vaseline (TM) (petroleum jelly) and microcrystalline wax.

Please amend the paragraph beginning at line 19 of page 16 as follows:

Examples of natural water-soluble polymers include plant polymers such as gum arabic, tragacanth gum, galactan, [[gua]] guar gum, carob gum, karaya gum, carageenan, tamarind gum, xanthane gum, pectin, agar, queenseed, marmelo, alga colloid (brown algae extract), starch (rice, corn, potato, wheat) and glycyrrhizic acid, microbial polymers such as xanthane gum, dextran succinoglucan and

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pluran, and animal polymers such as collagen, casein, albumin and gelatin.

Please amend the paragraph beginning at line 27 of page 22 as follows:

After inoculating the epidermic cells, the medium was changed to that containing either (1) 10  $\mu$ M ~~CGS23027A~~ CGS27023A (matrix metalloproteinase inhibitor) or (2) 300  $\mu$ M MMP-inhibitor (p-NH<sub>2</sub>-Bz-Gly-Pro-D-Leu-D-Ala-NHOH (FN-437) (BBRC, 1994, 199, p. 1442-1446) (acquired from Cabbiochem. Novabiochem Corporation) (matrix metalloproteinase inhibitor)) starting in the first week, and then replaced with medium containing the same type and same concentration of matrix metalloproteinase inhibitor every 2-3 days after that and cultured for 2 weeks. In addition, (3) similar culturing was carried out without adding matrix metalloproteinase inhibitor for use as a control.

Please amend the paragraph beginning at line 4 of page 23 as follows:

Those results are shown in Fig. 1. As is clear from the figure, although a basement membrane-like structure was not observed directly beneath the basal cells of the epidermis in control (3), in the case of adding matrix metalloproteinase inhibitors (1) CGS27023A compound or (2) ~~MMM-inhibitor~~ MMP-

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inhibitor, promotion of basement membrane formation was clearly observed.

Please amend the paragraph (Preparation Example 3) beginning at line 34 of page 28 as follows:

Preparation Example 3: Milky Liquid

	Wt%
Cetyl alcohol	1.0
Beeswax	0.5
Vaseline ( <u>Petroleum Jelly</u> )	2.0
Squalene	6.0
Dimethyl polysiloxane	2.0
Ethyl alcohol	5.0
Glycerin	4.0
1,3-butylene glycol	4.0
Active ingredient	0.1
Tranexamic acid	1.0
Polyoxyethylene (10) monooleic ester	1.0
Glycerol monostearic ester	1.0
Queenseed extract (5% aqueous solution)	20.0
Antiseptic	As suitable
Fragrance	As suitable
Ion exchanged water	As suitable

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Please amend the paragraph beginning at line 21 of page 29 as follows:

Glycerin and 1,3-butylene glycol were added to ion exchanged water, mixed and heated to 70°C (aqueous phase). Cetyl alcohol, beeswax, Vaseline (petroleum jelly), squalene, dimethyl polysiloxane, active ingredient (such as lipidure or CGS27023A), tranexamic acid, polyoxyethylene (10) monooleic ester, glycerol monostearic ester and antiseptic were prepared in the form of a mixture and heated to 70°C (oily phase). After adding the aqueous phase to the oily phase and performing preliminary emulsification, adding and stirring queenseed extract and ethyl alcohol and obtaining homogeneous emulsified particles using a homomixer, the emulsion was deaerated, filtered and cooled to obtain a milky liquid.

Please amend the paragraph (Preparation Example 4) beginning at line 34 of page 29 as follows:

Preparation Example 3: Milky Liquid

<u>Wt%</u>	<u>WT%</u>
Cetyl alcohol	1.0
Beeswax	0.5
Vaseline ( <u>Petroleum Jelly</u> )	2.0
Squalene	6.0
Dimethyl polysiloxane	2.0
Ethyl alcohol	5.0

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Glycerin	4.0
1,3-butylene glycol	4.0
Active ingredient	0.1
Tranexamic acid	1.0
Polyoxyethylene (10) monooleic ester	1.0
Glycerol monostearic ester	1.0
Queenseed extract (5% aqueous solution)	20.0
Antiseptic	As suitable
Fragrance	As suitable
Ion exchanged water	As suitable

Please amend the paragraph beginning at line 20 of page 30 as follows:

Glycerin and 1,3-butylene glycol were added to ion exchanged water, mixed and heated to 70°C (aqueous phase). Cetyl alcohol, beeswax, Vaseline (petroleum jelly), squalene, dimethyl polysiloxane, active ingredient (such as lipidure or CGS27023A), tranexamic acid, polyoxyethylene (10) monooleic ester, glycerol monostearic ester and antiseptic were prepared in the form of a mixture and heated to 70°C (oily phase). After adding the aqueous phase to the oily phase and performing preliminary emulsification, adding and stirring queenseed extract and ethyl alcohol and obtaining homogeneous emulsified particles using a homomixer, the emulsion was deaerated, filtered and cooled to obtain a milky liquid.

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